UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

October 31, 2011

MEMORANDUM

SUBJECT: Tributyl Tertradecyl Phosphonium Chloride (TTPC): Human Health Risk Assessment Scoping Document in Support of Registration Review.

PC Code(s): 128824	DP Barcode(s)/No(s): D394380
Decision No.: 455196	Registration Number (s): 83451-15, 83451-16, 83451-20
Petition No(s).: NA	Regulatory Action: Registration Review
Risk Assess Type: Single Chemical	Case No(s): 5111
TXR No.: NA	CAS No(s): 81741-28-8
MRID No(s).: NA	40 CFR: None

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EXECUTIVE SUMMARY

The Antimicrobials Division (AD) Registration Review Team has evaluated the status of the human health assessments for tri-n-butyl tetradecyl phosphonium chloride (TTPC) (registration review case 5111). One active ingredient (PC Code 128824) and three registered products exist in the TTPC case. TTPC is a quaternary phosphonium liquid biocide approved for use as an end-use product for control of algae, slime-forming bacteria, sulfate-reducing bacteria and fungi in industrial process water treatments (Use Site Category VIII). TTPC is delivered to industrial process waters using closed metered delivery systems; open pouring is prohibited. Examples of TTPC uses include water treatment in recirculating cooling water and process waters, heat exchange water systems, air washing systems, evaporative coolers, brewery pasteurizers, can warmers, hydrostatic sterilizers and retorts, pulp/paper/paperboard systems (non-food contact paper and paperboard manufacture of brown paper, sheet for corrugated board, Kraft paper, newsprint and similar paper), enhanced oil recovery systems (non-marine/non-estuarine use), oil and gas production transmission pipelines and systems, gas storage wells and systems, hydro-testing of pipelines and tanks, pipeline pigging and scraping operations and oil and gas well drilling and maintenance fluids. A petition for a new product use to control microbial growth in waters and on pipe surfaces in fire protection systems was recently submitted to the Agency on July 12, 2011. Although this is a new use, AD does not believe this use will change our conclusions on data needs or risk assessments for this human health registration review.

EPA examined the hazard and exposure databases for the TTPC case to determine whether changes in science policy or deficiencies in the databases materially affected the overall risk picture. TTPC was first registered as a pesticide in 1989. A Reregistration Eligibility Decision (RED) document has not been issued for TTPC since this chemical was registered after November 1, 1984. As part of the registration review process, the Agency reviewed the existing human health toxicology and exposure data from its initial registration in 2007, and the existing open literature.

On October 18, 2005, the Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) identified toxicological endpoints for non-dietary exposure scenarios. On September 7, 2007, AD developed an occupational exposure assessment for TTPC for registration (D340885 and D340886).

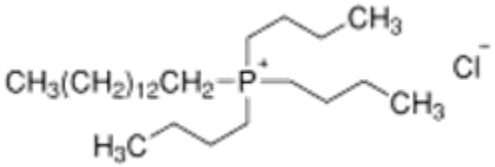
As a result of the closed mixing/loading, PPE, and low volatility, additional occupational handler assessments are not anticipated as needed for registration review. Dermal and inhalation post-application risks for water-treatment uses are likely to be minimal based on dilution, limited exposure contact, and low volatility. The labels for TTPC state that use is for industrial applications. Therefore, no residential assessments will be needed.

A dietary exposure assessment is not anticipated based on label restrictions specifying that TTPC is used on non-food applications. AD believes the concentration of TTPC in the drinking water will be minimal. However, EPA will make a determination at a later date whether or not a drinking water assessment is needed later based on the applicable

environmental fate data that AD required in the recent Environmental and Ecological Effects Scoping Document (D394379).

Section 1. Chemical Identity

TTPC is a quaternary phosphonium that is soluble in water, has a low water/octanol partition coefficient (Log K_{ow}), has a low vapor pressure and exhibits a low melting point. The active ingredient exists as a white solid at room temperature. Although it is not likely to be bioaccumulative in aquatic organisms, TTPC does not biodegrade in water and is stable in aqueous medium photolytically. TTPC is likely to be a persistent chemical in aqueous and soil media. No data are available for its binding capability to soils; however, since it is ionic in nature, TTPC is not likely to bind strongly with soils (D394379).

Table 1. Chemical Identity	
Common Name	Tri-n-butyl tetradecyl phosphonium chloride
Synonyms	none
PC Code	128824
CAS registry number	81741-28-8
Registration Review Case No.	5111
Structure	
Vapor Pressure	3.75E-8 mm Hg at 39ºC

Section 2. Toxicology

Acute Toxicity

TTPC purified grade active ingredient (PGAI) exhibits low acute oral and dermal toxicity (Toxicity Category III) and is corrosive to the eye (Toxicity Category I). An acute inhalation toxicity study for the TTPC PGAI was waived and Toxicity Category I assigned for inhalation. A formulated manufacturing-use product/end-use product (BELLACIDE 350, 50% TGAI) shows low acute oral toxicity (Toxicity Category III); however, it is acutely toxic via the dermal route (Toxicity Category I) and is highly irritating and corrosive to the eyes and skin (Toxicity Category I). The BELLACIDE 350 formulation (50% a.i.) was negative for dermal sensitization in the Guinea pig maximization test.

Table 2. Acute Toxicity Data for TTPC Purified Grade Active Ingredient (PGAI) and BELLACIDE 350 (50% a.i. EP/TGAI)			
Guideline Number Study Type	**MRID Number**	**Results**	**Toxicity Category**
81-1 Acute oral toxicity	00133040	LD_{50} = 611 mg/kg (M+F) (PGAI)	III
	00133041	LD_{50} = 1002 mg/kg (M+F) (BELLACIDE 350, 50% a.i. EP/TGAI)	
81-2 Acute dermal toxicity	00133042	LD_{50} = 4000 mg/kg (M+F) (PGAI)	III
	00133043	LD_{50} = Not Determined (ND); Animals sacrificed due to severe necrosis (M+F) (BELLACIDE 350, 50% a.i. EP/TGAI)	I (severe skin irritation)
81-3 Acute inhalation toxicity	Waived	--- (PGAI)	I
	Pilot Study (No MRID)	LD_{50} < 0.1mg/mL; severe pulmonary irritation and pneumonitis (BELLACIDE 350, 50% a.i. EP/TGAI)	
81-4 Acute eye irritation	00133044	Corrosive, Primary Irritation Index (PII) = 102.7 (mean unrinsed and rinsed eyes) (PGAI)	I
	00133045	Corrosive, primary irritation index (PII) = 60.2 (mean unrinsed) and 55.0 (mean rinsed eyes) (BELLACIDE 350, 50% a.i. EP/TGAI)	
81-5 Acute dermal irritation	00133046	Corrosive, extreme irritation, Primary Irritation Index (PII) = 7.7 (BELLACIDE 350, 50% a.i EP/TGAI)	I
81-6 Skin sensitization	46333002	Non sensitizer (BELLACIDE 350, 50% a.i. EP/TGAI)	NA

M = males; F = females; NA = not applicable

Subchronic Toxicity

In a 90-day drinking water study (MRID 41367301) conducted in the rat, TTPC produced significantly reduced body weights (up to 22% in males and 18% in females), various clinical signs (hunched posture, brownish discoloration on the muzzle and neck, prolapsed penis, piloerection, rough fur, foaming salivation, mucous salivation, and vaginal discharge), and significantly reduced food and water consumption at the LOAEL of 300 ppm (27.2 mg ai/kg/day for males and 32.2 mg ai/kg/day for females). The NOAEL established in this study is 100 ppm (8.66 mg ai/kg for males and 11.3 mg ai/kg for females). This study is classified acceptable-guideline for an oral subchronic toxicity study [OPPTS 870.3100] and is adequate for risk assessment purposes.

Prenatal Developmental Toxicity

In a prenatal rat developmental toxicity study (MRID 00133048, 40680704, 46721703), gavage administration of TTPC resulted in decreased body weight, body weight gain and food consumption in maternal animals at the LOAEL of 60 mg ai/kg/day. The maternal toxicity NOAEL is 30 mg ai/kg/day. The developmental toxicity NOAEL established in this study is 10 mg ai/kg/day based on the increased incidence of incomplete ossification of the fifth sternebrae in fetuses observed at the LOAEL of 30 mg ai/kg/day (in the absence of maternal toxicity). This study is classified acceptable-

guideline for a prenatal developmental toxicity study in rats [OPPTS 870.3700] and is adequate for risk assessment purposes.

In a prenatal rabbit developmental toxicity study (MRID 00133047, 40680705, 46721704); the maternal/developmental NOAELs and LOAELs are 3.75 and 11.25 mg ai/kg/day, respectively. Maternal toxicity consisted of decreased body weight gain and food consumption. Adverse developmental effects in rabbits included delayed ossification of the fore-limb and hind-limb phalangeal nuclei and significantly decreased fetal body weight for males. This study is classified acceptable-guideline for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700] and is adequate for risk assessment purposes.

Reproduction and Fertility Effects Toxicity

A reproduction and fertility effects toxicity study is not currently required to support the registered uses of TTPC containing pesticide products.

Chronic Toxicity

Chronic studies are not currently required to support the registered uses of TTPC containing pesticide products.

Carcinogenicity

A carcinogenicity study is not currently required to support the registered uses of TTPC containing pesticide products.

Mutagenicity

The data base for mutagenicity is considered adequate (see Table 3). TTPC (BELLACIDE 350, 50% a.i.) was negative for mutagenicity in a reverse gene mutation assay with bacteria and in DNA repair assays in rat hepatocytes and human fibroblasts. TTPC was also negative for chromosomal aberrations in hamsters in the *in vivo* micronucleus assay.

Neurotoxicity

An acute neurotoxicity study with cholinesterase measurements at the peak time of inhibition was required in 2007 based on the assumption that TTPC would behave similarly to an organophosphate pesticide. Rather, TTPC belongs to a different group of chemicals referred to as ionic liquids; specifically TTPC is a quaternary phosphonium compound that is manufactured as a liquid pesticide. In addition, the limited clinical signs (hunched posture and foaming/mucus salivation) observed in rats administered TTPC for 90-days via the drinking water occurred only at the highest dose tested (lack of a dose-response), are not present in other studies (e.g., animals treated with TTPC in acute and developmental toxicity studies show no salivation) and may not involve the cholinergic system/inhibition of cholinesterase activity (e.g., hunched posture). Therefore, the

Agency does not anticipate requiring neurotoxicity/cholinesterase studies conducted with TTPC.

Table 3. Mutagenicity Studies for TTPC	
Guideline, Study Type MRID/Classification	**Description of Results**
84-2 Reverse Bacterial Gene Mutation (Ames) Assay MRID 00133049/Accession No. 252019 Classification: Acceptable	BELLACIDE 350 (50% a.i.) did not cause a mutagenic effect at concentrations as high as 127.6 µg/0.1 ml (per plate) using *S. typhimurium* strains TA 98, 100, 1535, 1537 and 1538 with or without metabolic activation.
84-2 *In vivo* Nucleus Anomaly Cytogenetic Test in Chinese Hamster Bone Marrow MRID 40680706 Classification: Acceptable	BELLACIDE 350 (50% a.i.) is not mutagenic since it did not cause a dose-related or significant increase in anomalous nuclei when given via gavage once daily for 2 days to 6 male and 6 female Chinese hamsters at doses of 19, 38, or 76 mg/kg, in the absence of metabolic activation.
84-2 Unscheduled DNA Synthesis/Repair in Rat Hepatocytes) MRID 40680707/41185801 Classification: Acceptable	BELLACIDE 350 (49.85% a.i.) is not genotoxic since it did not cause DNA damage (lack of increases in grain counts which are indicative of repair) at doses up to cytotoxic levels of 5 µg/ml in the absence of metabolic activation.
84-2 Unscheduled DNA Synthesis/Repair in Human Fibroblasts MRID 40680708/41185802 Classification: Acceptable	BELLACIDE 350 (49.85% a.i.) is not genotoxic since it did not cause DNA damage at the highest 9 µg/ml nontoxic dose in the absence of metabolic activation. Test results under conditions of no metabolic activation are considered acceptable. However, this type of mutagenicity study is satisfied by MRID 40680707.

Toxicity Endpoint Selection for Human Health Assessments

On October 18, 2005, the Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) identified toxicological endpoints for non-dietary, short-term (ST)/intermediate-term (IT) incidental oral (residential), dermal (occupational/residential) and inhalation (occupational/residential) exposure scenarios. The ST/IT NOAEL selected for these non-dietary risk assessments was 8.66 mg/kg/day based on the toxicities observed at the LOAEL in the 90 day rat oral toxicity study. The target margin of exposure (MOE) for ST/IT exposures via the incidental oral, dermal, routes was set at 100 based on uncertainty factors (UFs) of 10x for inter-species extrapolation and 10x for intra-species variation. A default absorption factor of 100% was used for the dermal and inhalation exposure risk assessments since no absorption study data are available. For short- and intermediate-term inhalation exposure scenarios, an additional UF of 10 was applied to the endpoint based on use of an oral endpoint to assess inhalation hazard. Consequently, the TTPC target MOE for inhalation was set at 1000 (10x for inter-species extrapolation, 10x for intra-species variation, and 10x for extrapolation from an oral toxicity study for inhalation risk assessments).

However, in 2007, the registrant submitted a label amendment application to add two new uses to the existing BELLACIDE 350 label as well as new information showing a low vapor pressure for TTPC technical grade active ingredient. These actions initiated a re-evaluation of the toxicity endpoints, UFs, and target MOEs previously selected for the

active ingredient, TTPC. For the proposed new uses of BELLACIDE 350 (50% a.i.), no additional toxicity data, application of an additional 10x for inhalation exposures, or inhalation risk assessments were required to address use of this product in enhanced oil recovery systems and non-food contact pulp and paperboard processing. However, this decision (Memorandum: S. Malish to V. Noble, June 31, 2007) does not negate the need to assess potential risks for other existing labeled uses of pesticide products containing TTPC.

Anticipated Mammalian Toxicology Data Needs

Initially, the ADTC (Memorandum: T. McMahon to N. Cook, November 5, 2005) identified two toxicology data gaps for TTPC; a 28-day repeated-dose inhalation toxicity study with an associated range-finding study (to assess occupational short-term and intermediate-term inhalation risk because of the presumed high vapor pressure of TTPC) and an acute neurotoxicity study with cholinesterase measurements at the peak time of inhibition (because TTPC was considered an organophosphate pesticide and cholinesterase activity was not measured in the available toxicity studies).

The data gap for a 28-day inhalation toxicity study was negated in 2007 due to (1) a correction in the vapor pressure value for TTPC (a low vapor pressure is currently reported for TTPC) and (2) removal of the labeled use of BELLACIDE 350 (50% TTPC a.i.) in decorative fountains. As for the acute neurotoxicity study with cholinesterase measurements data gap, the Agency no longer requires this special study because clinical signs (hunched posture and foaming/mucus salivation) were observed in only one toxicity study, were not dose-related and/or may not involve the cholinergic system/inhibition of cholinesterase activity.

Although unlikely, dietary exposures to TTPC via drinking water may occur in the event of an industrial down-the-drain discharge in which contaminated water could pass through waste water treatment facilities into drinking water, be discharged directly to surface water that is subsequently treated and/or migrate into residential groundwater wells. If the additional environmental fate data as required by the Agency's registration review of TTPC shows this active ingredient and/or any of its' degradates to be persistent in drinking water, additional toxicity studies (e.g., a reproduction and fertility effects study, a chronic toxicity study, carcinogenicity studies in two species or tier 1 toxicity studies for degradates of toxicological concern) may be required.

Section 3. Dietary Assessment

Dietary (Food)

According to the existing labels, TTPC may be used as a slimacide for pulp, paper and paperboard mills and water systems; however, the label restricts the use to nonfood applications and TTPC was not cleared for any indirect food contact use by FDA. As a result, no dietary exposure assessment is anticipated to be needed.

Drinking Water

Although it is expected that drinking water exposures are likely to be infrequent, dietary exposures via drinking water may occur in the event of a down-the-drain discharge. The contaminated water could pass through wastewater treatment facilities into the drinking water or may be discharged directly to surface water which is later treated. However, at this time there are no available environmental fate data to determine whether TTPC can pass through wastewater treatment facilities into drinking water or migrate into residential groundwater wells as a result of its current use patterns. Upon receipt and review of the environmental fate data the Agency anticipates requiring, the Agency will determine the need for a down-the-drain drinking water assessment.

Section 4. Occupational/Residential Exposure

TTPC is the active ingredient in three registered products. These products are formulated as liquid soluble concentrates for use in industrial processes and water systems (Use Site Category VIII). The industrial process and water system category includes uses such as recirculating cooling and process water systems, air washers and industrial air scrubbing systems, heat transfer systems, pulp and paper and paperboard mills, enhanced oil recovery systems, fire protection systems, oil and gas production and transmission pipelines and systems, gas storage wells and systems, hydrotesting, pipeline pigging and scraping operations, drilling and workover and fracturing fluids.

The end-use products contain 5 to 50% active ingredient (a.i.), the labels of which explicitly states that the biocide is to be metered into water via a fully closed system. Labeling also requires PPE such as coveralls worn over long-sleeved shirt, goggles, face shield, chemical resistant gloves and footwear in case of leaks or breaks in the closed delivery system.

The Agency did an open literature search and did not identify any relevant exposure studies in the existing literature that could be used to supplement the existing Agency exposure database. There are minimal potential exposures for closed mixing/loading systems.

The vapor pressure is 3.75E-8 mm Hg at 39ºC. As a result of the closed mixing/loading, PPE for protection against leaks/malfunctions, and low volatility; additional occupational handler assessments are not anticipated as needed for registration review. Dermal and inhalation post-application risks for water-treatment uses are likely to be minimal based on dilution, limited exposure contact, and low volatility.

The labels for TTPC are for industrial applications and no consumer products are treated. Therefore, no residential assessments will be needed.

Section 5. Aggregate and Cumulative Exposure

In examining aggregate exposure, EPA takes into account the available and reliable information concerning exposures to residues in food and drinking water, and non-

occupational pesticide exposures. EPA does not expect that an aggregate exposure assessment will need to be initiated.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to TTPC and any other substances and TTPC does not appear to produce a toxic metabolite produced by other substances. For the purposes of registration review, therefore, EPA has not assumed that TTPC has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Section 6. Incidents

There have been no human incidents reported in any of the OPP databases associated with exposure to TTPC.

Section 7. Anticipated Data Needs

The Antimicrobial Division (AD) does not anticipate the need for any additional toxicity or exposure studies for TTPC for registration review.

Section 8. Tolerances

There are no pesticide tolerances or exemptions from the requirement of tolerance for TTPC established by either EPA or FDA.

Section 9. Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of the registration hazard assessment for TTPC, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), TTPC is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. TTPC is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Accordingly, as part of registration review, EPA will issue future EDSP orders/data call-ins, requiring the submission of EDSP screening assays for TTPC. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Section 10. References

D394379. Tri-n-Butyl Tetradecyl Phosphonium Chloride, Product Chemistry, Environmental Fate, and Ecological Effects Scoping Document for Registration Review. Memorandum from S.Gowda, W. Erickson, and N. Shamim to E. Blair.

D340885 and D340886. Occupational Exposure Assessment for TTPC: Proposed Label Amendments to Add New Use Sites for Bellacide 350 (50% TTPC) and Bellacide 355 (5% TTPC) Industrial End-Use Products. Memorandum from D. Aviado, U.S. EPA to D. Edwards, U.S. EPA. September 10, 2007.

D394470. Tri-n-Butyl Tetradecyl Phosphonium Chloride**:** Toxicology Chapter/Hazard Characterization for the Human Health Assessment Scoping Document for Registration Review of TTPC (Case No. 5111). Memorandum from M. Centra, U.S. EPA to N. Mottl and E.Blair, TXR No.: 1003219. October 25, 2011.